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UCLA RESEARCHERS IDENTIFY LEUKEMIA STEM CELLS AND THE ALTERATIONS THAT CAUSE NORMAL CELLS TO BECOME CANCEROUS

Stem cell researchers at UCLA have identified a type of leukemia stem cell and uncovered the molecular and genetic mechanisms that cause normal blood cells to become cancerous.

The discovery may lead to the development of new therapies that target these leukemia stem cells, attacking the disease at its very root and killing the early cells that give rise to mature cancer cells. The study appears in the May 22, 2008 issue of the journal Nature.

Recent studies suggest that cancer stem cells may contribute to development of several types of cancer, cancer relapse and drug resistance. New anti-cancer therapies will need to kill or stop the cancer stem cell from proliferating to battle the cancer most effectively. Therapies targeting the derivatives of the cancer stem cell, the mature cancer cells, are not as effective and leave the "seeds" of the disease untouched.

If scientists could understand the biology of cancer stem cells and find a way to kill them, new and much more effective therapies could be developed to seek out and eliminate the cancer stem cells, robbing the cancer of its ability to re-grow and crippling, if not completely eliminating it, from the body.

Led by Dr. Hong Wu, a professor of medical and molecular pharmacology and a scientist with the Eli and Edythe Broad Center of Regenerative Medicine and Stem Cell Research, the UCLA team has for the first time identified and isolated the cancer initiating cells responsible for a type of leukemia known as acute T-lymphoblastic leukemia, an aggressive and deadly cancer that occurs both in children and adults. Using a genetically engineered model, the team also discovered the key steps that turn normal blood cells into malignant leukemia stem cells, providing potential targets for news therapies.

"One of the main challenges in cancer biology is to identify cancer stem cells and define the molecular and genetic events required for transforming normal cells into cancer stem cells," said Wu, senior author of the Nature study and also a researcher at UCLA's Jonsson Comprehensive Cancer Center.

The origin of cancer stem cells is not entirely clear. Normal tissue stem cells – in this case blood cells - are likely targets for insults that can initiate cancer due to their long

life span, necessary for the accumulation of the multiple genetic or epigenetic changes required for malignant transformation. However, mutated stem cells do not necessarily become cancer stem cells. Recent experimental evidence suggests that cancer can originate from either a self-renewable stem cell population or their more differentiated progenies that have acquired self-renewal capacity due to accumulated mutations. In a leukemia model generated for this study, the leukemia stem cells carry T lymphocytic marker, suggesting a T-cell origin.

The UCLA team wanted to know how blood stem cells become cancerous and studied the cells at the molecular and genetic level to uncover those mechanisms.

"We know that cancer formation requires multiple genetic or molecular alterations," said Wei Guo, the first author of the study and a postdoctoral associate in Wu's lab who received support from the California Institute of Regenerative Medicine. "Our study suggests that such alterations may happen at the level of cancer stem cells."

The alterations found that collaboratively contribute to leukemia stem cell formation were the deletion of the PTEN tumor suppressor gene, a chromosomal translocation involving c-myc, an oncogene, and the activation of a signaling molecule, called beta-catenin, that is known to be involved in stem cell self-renewal.

"Interestingly, the events that we have identified in our model system have also been found in human leukemia patients," Wu said.

Wu and her team currently are testing therapies that target the alterations they discovered, hoping to interrupt the process that causes the normal blood cells to become leukemia stem cells, thereby stopping the cancer. They're also looking for other alterations that might be at play in resistance to these targeted therapies.

Dr. Luisa Iruela-Arispe, a professor of molecular, cell and developmental biology and a Broad Stem Cell Center researcher, also is a co-author of the Nature paper.

The stem cell center was launched in 2005 with a UCLA commitment of $20 million over five years. A $20 million gift from the Eli and Edythe Broad Foundation in 2007 resulted in the renaming of the center. With more than 150 members, the Eli and Edythe Broad Center for Regenerative Medicine and Stem Cell Research is committed to a multi-disciplinary, integrated collaboration of scientific, academic and medical disciplines for the purpose of understanding adult and human embryonic stem cells. The institute supports innovation, excellence and the highest ethical standards focused on stem cell research with the intent of facilitating basic scientific inquiry directed towards future clinical applications to treat disease. The center is a collaboration of the David Geffen School of Medicine, UCLA's Jonsson Cancer Center, the Henry Samueli School of Engineering and Applied Science and the UCLA College of Letters and Science. To learn more about the center, visit our web site at http://www.stemcell.ucla.edu/.

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